ODAC Briefing Document

NDA 22481
Pixuvri (pixantrone)

FDA Briefing Document
Oncologic Drugs Advisory Committee Meeting
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Pixuvri (pixantrone)
Applicant: Cell Therapeutics, Inc.

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1. Introduction

Cell Therapeutics has submitted a new drug application for the use of pixantrone in patients with aggressive non-Hodgkin's lymphoma (NHL) who have received 2 or more prior lines of therapy. This application is supported by a randomized Phase 3 study which enrolled substantially fewer patients than had been planned and a single arm Phase 2 study. Issues in the review of this application include the following:

- The level of evidence necessary to draw conclusions from this Phase 3 study and the reliability of these conclusions; and
- Substantial hematologic and cardiac toxicity.

2. Background

Pixantrone is an aza-anthracenedione with structural similarity to mitoxantrone. In pre-clinical models, pixantrone displayed enhanced activity and decreased cardiotoxicity with decreased free radical formation. Clinically, pixantrone has been developed for the treatment of NHL with an additional single trial in acute leukemia.

Table 1 shows the products that have been approved for use in patients with relapsed or refractory NHL. A number of older products (cyclophosphamide, doxorubicin, vinblastine and vincristine) have been given a general indication for the treatment of lymphoma.

Table 1: Products Indicated for Relapsed/Refractory (R/R) NHL

Product	Indication	Trial	Findings
Rituximab 1997	R/R CD20+ low grade or follicular NHL	Single arm trials in R/R low grade, CD20+ NHL	ORR: 38-57% Median duration: 11.2-15 mos
Ibritumomab Tiuxetan (Zevalin) 2002	R/R CD20+ low grade or follicular NHL	Single arm trial in R/R low grade or follicular NHL Zevalin vs. rituximab in pts w/ R/R low grade or follicular NHL	ORR: 74% Median duration: 6.4 mos ORR: 83% Zevalin vs. 55% Rituximab Median duration: 14.3 mos Zevalin vs. 11.5 mos Rituximab
Tositumomab and ^{131}I-Tositumomab (Bexxar) 2003	R/R CD20+ low grade, follicular or transformed NHL	Single arm trials in R/R low grade, follicular or transformed NHL	ORR: 68%, 47% Median duration: 16 mos, 12 mos
Bortezomib 2006	Mantle cell lymphoma 1 prior therapy	Single arm trial in R/R mantle cell lymphoma	ORR: 31% Median duration: 9.3 mos
Pralatrexate 2009	R/R peripheral T-cell lymphoma	Single arm trial in R/R peripheral T-cell lymphoma	ORR: 27% Median duration: 9.4 mos

Note that bortezomib and pralatrexate were each approved on the basis of response rate in relapsed or refractory disease in single arm trials of patients with an uncommon NHL subtype.

Regulatory History

The pivotal trial, PIX301, was discussed at an End of Phase 2 meeting on October 8, 2003. At this meeting, FDA stated, "Accelerated approval could be based on an interim analysis of a surrogate endpoint with completion of the trial demonstrating an improvement on a clinical benefit endpoint (survival or symptom benefit)." FDA recommended that the trial assess complete response and the duration of complete response. Subsequently, agreement was reached concerning a Special Protocol Assessment for PIX301. On March 28, 2008, CTI notified the FDA of an early halt to enrollment for PIX301. The study was not stopped at a planned interim analysis and early study stopping invalidated the applicant's Special Protocol Assessment. The applicant subsequently analyzed their data and began submission of a rolling NDA on April 13, 2009 with the last module submitted on June 22, 2009.

3. Clinical/Statistical - Efficacy

The applicant submitted the following studies of the efficacy of single agent pixantrone in patients who have progressed following at least 2 prior therapies.

1. **PIX301:** Pixantrone versus Other Chemotherapeutic Agents for Third-Line Single Agent Treatment of Patients with Relapsed Aggressive Non-Hodgkin's Lymphoma: A Randomized, Controlled, Phase III Comparative Trial (N = 140)

2. **AZA-II-01:** A Phase II Study of BBR 2778 in Patients with Relapsed, Aggressive NHL (N = 33)

Phase 3 Study: PIX301

Eligibility
Patients entering this trial had relapsed or refractory, aggressive NHL including:

1. Grade 3 follicular lymphoma;
2. Transformed lymphoma;
3. Diffuse large B-cell lymphoma;
4. Peripheral T-cell lymphoma; and
5. Anaplastic large cell lymphoma (systemic, T/null cell).

Histology at study entry was determined by the site pathologist. A central review of histology was subsequently conducted, but was not an entry requirement.

Patients must have received at least 2 prior combination chemotherapy regimens.

- The first line regimen must have contained an anthracycline/anthracenedione.
- Total doxorubicin equivalent dose must be < 450 mg/M^2 with EF $\geq$ 50%.
- Patients must have been sensitive to their last anthracycline or anthracenedione. This was defined as a previous response or relapse after a response lasting $\geq$ 6 months.
- Prior rituximab was only required if it was considered the standard of care in that region.

Treatment

PIX301 was conducted from October 2004 to August 2008. Stratification factors included region, International Prognostic Index (IPI) score, and prior transplant. Patients were randomized 1:1 to single agent pixantrone or the following choice of comparators.

1. Oxaliplatin
2. Ifosfamide
3. Vinorelbine
4. Etoposide (PO/IV)
5. Mitoxantrone
6. Gemcitabine (only at U.S. sites)
7. Rituximab (only at U.S. sites)

Patients were treated for up to 6 cycles.

Safety Monitoring

Routine laboratories were obtained on Days 1, 8 and 15 of each cycle. Assessments of the left ventricular ejection fraction (EF) and serum troponins were performed at baseline, after Cycles 2 and 4, at the end of treatment, and 6 months after the completion of treatment. Study drug was discontinued in patients with symptomatic heart failure or with a decrease in EF $\geq$ 20% or to an absolute level $\leq$ 40%. EKGs were obtained at baseline, Day 1 of Cycles 1 and 2, and at the end of treatment. Disease assessments were performed every 8 weeks during the treatment period, regardless of regimen. Patients were followed up to 18 months after completion of chemotherapy.

Independent Review

Two independent review committees and an independent assessment panel were used by the applicant.

- Independent Review Committee (pathology IRC): The pathology IRC included 2 pathologists. The 2 pathologists reviewed each patient's slides. Post hoc, if the 2 pathologists disagreed, a 3rd pathologist adjudicated their findings.

- Independent Review Committee (radiology IRC): The radiology IRC included one independent radiologist who reviewed all scans.

- Independent Assessment Panel (IAP): The IAP included a different independent radiologist, an oncologist and a pathologist. They assessed the patient images along with relevant clinical information to determine response. Response was assessed according to the International Working Group criteria (J Clin Oncol 1999 17:1244). When new information became available (the type/nature of the additional information was not recorded) images could be reread by the IAP. The results of the last review by the IAP were used in the analysis of the primary endpoint. The majority opinion was used. If a majority opinion was not reached, the lowest level of response was assigned.

Statistical Plan

The study planned to accrue 320 patients and 189 sites were open to enrollment. However, only 66 sites accrued patients and the trial was stopped prematurely due to poor accrual following enrollment of 140 patients. The applicant stated that enrollment was hampered by investigator reluctance to enroll patients and that many investigators preferred to use either multi-agent chemotherapy or supportive care in this 3rd line population.

The primary analysis was an assessment of the difference in complete response and unconfirmed complete response (CR/CRu) by the IAP in the intent to treat population. There was no plan for alpha spending for secondary endpoints. Secondary endpoints included overall survival, overall response rate in patients with responses lasting $\geq$ 4 months vs. < 4 months, and progression-free survival. Duration of complete response and overall response rate were exploratory endpoints.

Patient Disposition

The table below provides information on patient disposition. Note that almost twice as many patients discontinued due to an adverse event (AE) in the pixantrone arm compared to control, but that there was an increase in discontinuations due to progressive disease and patient/investigator decision in the control arm of this open label study.

Table 2: Patient Disposition

	Pixantrone N = 70	Comparator N = 70
Enrolled	70	70
Treated	68 (97.1%)	67 (95.7%)
Completed 6 Cycles	20 (28.6%)	16 (22.9%)
Premature Discontinuation	50 (71.4%)	54 (77.1%)
Progressive Disease	28 (40.0%)	39 (55.7%)
Adverse Event	16 (22.9%)	9 (12.6%)
Lost to Follow Up	2 (2.9%)	0
Patient/Investigator Decision	3 (4.3%)	6 (8.6%)
Other	1 (1.4%)[1]	0

[1]Did not meet eligibility

Patient Demographics

Patient demographics were well balanced between arms. Median age was 60 years on the pixantrone arm and 58 years on the comparator arm. Approximately 2/3 of patients were male and most (65.9% pixantrone, 62.9% comparator) were Caucasian. Most patients were accrued outside of the US, with 8 patients accrued from 6 sites in the US. The 8 US patients differed from the remainder of the population in that they were more heavily pre-treated (50% had received $\geq$ 6 prior regimens compared to 5% of the total population) and were more likely to have undergone prior stem cell transplant (37.5% of US patients compared to 15.0% of the total population). Accrual by region is shown in the table below.

Table 3: Patient Demographics		
	Pixantrone N = 70	Comparator N = 70
Geographic Region		
Eastern Europe	19 (27.1%)	17 (24.3%)
South America	19 (27.1%)	18 (25.7%)
Western Europe	19 (27.1%)	19 (27.1%)
India	9 (12.9%)	12 (17.1%)
United States	4 (5.7%)	4 (5.7%)

Disease Characteristics

Table 4 provides information on baseline disease characteristics. Baseline tumor burden was calculated by adding the cross-products of IAP-determined baseline target lesion measurements.

Table 4: Disease Characteristics		
	Pixantrone	Comparator
	N = 70	N = 70
Prior Therapy		
Median Number of Prior Regimens (25-75)	3 (2-3)	3 (2-3)
Median Doxorubicin Equivalents (25-75)[1]	292.9 mg/M^2 (228.5-362.6)	315.5 mg/M^2 (279.3-400.0)
Prior Rituximab	37 (52.9%)	39 (55.7%)
Prior Stem Cell Transplant	11 (15.7%)	10 (14.3%)
	N = 70	N = 69
Median IPI Score (25-75)[2]	2 (1-3)	2 (2-3)
	N = 67	N = 68
Median Time Since Diagnosis (25-75)	32.0 months (19.0-50.9)	31.6 months (19.8-51.7)
	N = 69	N = 63
Median Baseline Tumor Burden (25-75)	24.1 cm^2 (7.3-48.3)	23.1 cm^2 (9.3-52.4)

[1]The formula (0.833 x daunorubicin mg/M^2) + (0.67 x epirubicin mg/M^2) + (5 x idarubicin mg/M^2) + (4 x mitoxantrone mg/M^2) + doxorubicin mg/M^2 was used to calculate doxorubicin equivalents.
[2]International prognostic scoring system includes age, tumor stage, LDH, PS and extra nodal involvement

Table 5 provides patient histology as assessed by the site pathologist at study entry and by central review. A consensus was not reached for 4 patients on the pixantrone arm and 2 patients on the comparator arm. A non-aggressive histology was found, by central review, in 12/64 (18.8%) patients on the pixantrone and 16/66 (24.2%) patients on the comparator arm. This level of disagreement is consistent with the literature (Pathol Res Pract 1989 184:242, Cancer 1977 39:1071). Among patients with a non-aggressive histology by central review, 5 patients on the pixantrone and 1 patient on the comparator arm achieved a CR/CRu.

Table 5: Tumor Histology				
	Pixantrone Histology N = 70		Comparator Histology N = 70	
	At Entry	By Central Review	At Entry	By Central Review
Diffuse Large B-Cell Lymphoma	54 (77.1%)	38 (54.3%)	51 (72.9%)	40 (57.1%)
Transformed Indolent Lymphoma	10 (14.3%)	6 (8.6%)	9 (12.9%)	3 (4.3%)
Peripheral T-Cell Lymphoma	3 (4.3%)	1 (1.4%)	7 (10.0%)	3 (4.3%)
Anaplastic Large Cell Lymphoma	2 (2.9%)	1 (1.4%)	1 (1.4%)	0
Grade 3 Follicular Lymphoma	1 (1.4%)	2 (2.9%)	2 (2.9%)	2 (2.6%)
Aggressive Histology NOS[1]		4 (5.7%)		2 (2.6%)
Non-Aggressive Histology[2]		12 (17.1%)		16 (22.9%)
Not Done		6 (8.6%)		4 (5.7%)

[1]At least 2 central reviewers reported eligible aggressive histology, but no consensus was reached on the subtype.
[2]At least 2 central reviewers reported ineligible histology.

Comparator Therapy

On the comparator arm, investigators could choose among several single agent options. The table below provides a list of those options and information on the frequency of their use in the 67 patients treated on the comparator arm (70 randomized). Note that gemcitabine and rituximab were only options for patients enrolled in the US.

Table 6: Comparator Arm	
Comparator	Comparator Arm N = 67
Oxaliplatin	30 (42.9%)
Ifosfamide	12 (17.1%)
Vinorelbine	11 (15.7%)
Etoposide (PO/IV)	5 (7.1%)/4 (5.7%)
Mitoxantrone	4 (5.7%)
Gemcitabine	1 (1.4%)
Rituximab	0

Protocol Violations

There were a limited number of major protocol violations recorded on the Phase 3 trial. Of primary concern is the rereading of response assessments by the IAP (see below).

Primary Endpoint

The table below shows the primary analysis by the IAP in the ITT population.

Table 7: Primary Analysis by IAP in ITT Population		
Response Rate	Pixantrone N = 70	Comparator N = 70
CR/CRu	14 (20.0%)	4 (5.7%)
p-value (Fisher's exact)		0.021

The planned sample size was 320. However, the study stopped early at an unplanned time point, due to poor accrual. A higher level of evidence is usually required in trials which

discontinue prior to the final analysis. Based on the Rho family error spending function (Rho parameter = 2) used in the sponsor's statistical analysis plan and with 44% of planned enrollment, the significance level allocated for the submitted analysis would be 0.0096 (0.0014 based on the O'Brien-Fleming-type error spending function). Therefore, the submitted primary analysis would not be significant.

Sensitivity Analyses

The applicant provided investigator (INV), Independent Review Committee (IRC), and Independent Assessment Panel (IAP) review of the primary endpoint. While these findings are similar, they illustrate one of the issues surrounding the interpretation of this trial. That is, while the p-value for the primary analysis is 0.021, a change in the assignment of response for even a single pixantrone-treated patient who achieved an IAP-determined CR/CRu would greatly affect the level of statistical significance. For example, 1 less CR/CRu on the pixantrone arm would have resulted in a p-value of 0.036 rather than 0.021, while 2 fewer patients with a CR/CRu would have resulted in a p-value of 0.06.

Table 8: Primary Endpoint by Investigator and Independent Review

	Pixantrone N = 70	Comparator N = 70
CR/CRu		
IAP	14 (20.0%)	4 (5.7%)
IRC Radiology	15 (21.4%)	5 (7.1%)
INV	12 (17.1%)	4 (5.7%)

Of greater concern is the re-reading of some of the scans by the IAP. The IAP carried out up to 4 readings of the same scan (the primary analysis used the last reading). Re-readings occurred in all patients who had a scan prior to July, 2006 and were conducted whenever new information became available (new information not recorded). The types of scans sent for re-evaluation were closely examined for bias (increased re-reading in one arm or increased re-readings of scans with a partial response). Bias was not detected. However, re-reads resulted in a change in the assessment of response to CR/CRu in 2 patients on the pixantrone and 1 patient on the comparator arm. Given these uncertainties in the assessment of response, some scans will be evaluated by an independent radiologist in January of 2010.

A sensitivity analysis was conducted in all patients with aggressive lymphoma by central pathology review. By IAP assessment, CR/CRu was seen in 8/52 (15.4%) patients on the pixantrone arm and 3/50 (6.0%) patients in the comparator arm. An additional sensitivity analysis is the rate of confirmed CR/CRu (the International Working Group criteria do not require a confirmatory scan). By IAP assessment, confirmed CR/CRu was seen in 11/70 (15.7%) patients on the pixantrone arm and in 3/70 (4.3%) comparator patients.

Subgroup Analyses

A large number of subgroup analyses were conducted. Given the number of patients who attained the primary endpoint, these results are unstable and subset analyses will not be discussed. However, CR/CRu was seen in patients who had received rituximab and in those

who had undergone stem cell transplant. Of concern, no patients enrolled in the US attained a CR or CRu.

Additional Endpoints

Censoring patients with 2 consecutive missing scans immediately prior to their last assessment results in the duration of CR/CRu shown in Table 9.

Table 9: Duration of Complete Response		
	Pixantrone N = 14	Comparator N = 4
Duration of CR/CRu	5.5 months	3.4 months

Table 10 shows the analysis of overall survival using data provided in the 120 day safety update. At that time, 8 patients on the pixantrone and no patients on the comparator arm remained evaluable. Table 10 also shows the results of the analysis of response rate at the initial data cutoff. Response rate has typically served as the basis for accelerated approval in lymphoma. Note that response rate was not a primary or secondary endpoint of this trial.

Table 10: Additional Endpoints		
	Pixantrone N = 70	Comparator N = 70
Overall Survival		
Number of Events	44 (62.9%)	47 (67.1%)
Median Overall Survival	10.2 months	6.9 months
Hazard Ratio (p-value)		0.82 (0.35)
Response Rate		
ORR (CR+CRu+PR)	26 (37.1%)	10 (14.3%)

Supportive Study: AZA-II-01

The applicant also submitted AZA-II-01: A Phase II Study of BBR 2778 in Patients with Relapsed Aggressive NHL. This study enrolled 33 patients with diffuse large B-cell, mantle cell, transformed follicular, and nodal marginal zone lymphoma. Relapse was not required and patients entering this study had received 0-3 prior chemotherapeutic regimens. However, anthracycline/anthracenedione sensitivity was required along with an EF $\geq$ 30%.

Patients received pixantrone 85 mg/M^2 on Days 1, 8, and 15 every 28 days. MUGA scans were performed every 2 cycles in patients with a baseline EF $\geq$ 50% (N = 24). Study drug was discontinued in patients with symptomatic HF or with a decrease in EF $\geq$ 10% to a level $\leq$ 50%. Patients with a baseline EF 30 to < 50% (N = 9) underwent MUGA scans each cycle. In these patients, study drug was discontinued in patients with symptomatic HF or with a decrease in EF $\geq$ 10% to a level < 30%. Troponins were assessed at baseline and on Day 15 of each cycle. Tumor assessments were performed at baseline and then every other cycle. Confirmation of response was required.

This trial did not use the IWG criteria and the table below provides the response rate (CR+PR by WHO/UICC criteria) in the supportive trial. There were 5 additional patients with unconfirmed PR.

Table 11: Response Rate in the Supportive Trial	
	Pixantrone N = 33
INV ORR (CR+PR)	9/33 (27.3%)
CR	5
PR	4

4. Safety

The table below provides an overview of the pixantrone safety database, including the number of patients who received pixantrone at the proposed dose and schedule.

Table 12: Studies of Pixantrone					
Study #	Population	Design	Dose (mg/M^2)	# Any Pixantrone	# Pixantrone 85 mg/M^2 d 1, 8, 15
AZA-I-01	Solid Tumors	Dose Escalation	20-240 d 1	24	0
AZA-I-02	Solid Tumors	Dose Escalation	5-112.5 d 0, 7, 14 q 28 d	30	0 (4 received 75 mg/M^2)
AZA-I-03	NHL, CLL	Dose Escalation	5-84 d 0, 7, 14 q 28 d	26	6
AZA-I-04	Solid Tumors	Dose Finding	180 or 270 q wk	4	0
AZA-I-05	NHL	Activity in Combination	80 d 1 q 21 d	19	0
PIX109	AML	Dose Escalation	80-110 d 1-3 q 21 d	12	0
AZA-I-06	NHL	Combination Dose Escalation	80-120 d 2 q 28 d	28	0
AZA-I-07	NHL	Combination Dose Escalation	80-180 d 1 q 21 d	35	0
AZA-I-07	NHL	Activity in Combination	150 d 1 q 21 d	30	0
AZA-II-01	**NHL**	**Activity**	**85 d 1, 8, 15 q 28 d**	**33**	**33**
AZA-II-02	NHL	Activity in Combination[1]	80 d 1 q 21 d	19	0
AZA-III-02	NHL	Pixoxantrone + R vs. Rituximab	90 d 1	20	0
PIX301	**NHL**	**Single Agent vs. Comparators**	**85 d 1, 8, 15 q 28 d**	**68**	**68**
Total				**348**	**111**

[1]Followed by stem cell transplant

Exposure

In the Phase 3 trial, dosing delays or interruptions were seen in 54.4% of pixantrone patients. In the comparator arm, where a wide variety of medications were used, 28.4% of patients required a dosing delay or interruption. Further, 51.5% of patients on the pixantrone arm and 26.9% of patients in the comparator arm required G-CSF to maintain dosing. The median duration of treatment was 15.1 weeks on the pixantrone arm and 12.1 weeks on the comparator arm. Information on long term use or the late effects of pixantrone is limited.

Safety Overview

Table 13 provides a safety overview of adverse events on the Phase 3 trial. Given the various comparators used, some level of imbalance is expected between the arms. However, note that deaths, SAEs, and grade 3-4 events were all more common on the pixantrone arm.

Table 13: Safety Overview of the Phase 3 Trial

Event	Pixantrone N = 68	Comparator N = 67
Death due to an Adverse Event[1]	12 (17.6%)	5 (7.5%)
Discontinuation due to an Adverse Event	25 (36.8%)	21 (31.3%)
Serious Adverse Events	35 (51.5%)	30 (44.8%)
Grade 3-4 Adverse Events	52 (76.5%)	35 (52.2%)
Grade 1-4 Adverse Events	66 (97.1%)	61 (91.0%)

[1]Other than AEs coded as disease progression

Deaths and Discontinuations

Table 14 provides information on the causes of deaths and discontinuations due to adverse events other than disease progression. Given the increase in deaths and discontinuations due to cardiac events as well as the drug class, the cardiotoxicity of pixantrone is discussed below.

Table 14: Deaths and Discontinuations

	Pixantrone N = 68	Comparator N = 67
Deaths Due to an Adverse Event		
All	12 (17.6%)	5 (7.5%)
Cardiac Failure	3	1
Infection	3	2
Respiratory Failure/ARDS	3	0
Other[1]	3	2
Adverse Events Leading to Discontinuation in ≥ 3 Patients		
All	25 (36.8%)	21 (31.3%)
Neutropenia	5	0
Cardiac Failure	3	1
Decreased Ejection Fraction[2]	3	0
Pleural Effusion	1	3
Thrombocytopenia	0	5

[1]Includes obstructive airway disorder, MDS, pulmonary venous thrombosis on the pixantrone arm and obstructive airway disorder and renal failure on the comparator arm.
[2]Includes patient 118, coded as LV dysfunction but with decreased EF only.

There was one discontinuation due to febrile neutropenia on the pixantrone arm.

Serious Adverse Events/Grade 3-4 Adverse Events

Serious adverse events and grade 3-4 events included the consequences of bone marrow suppression (7.4% incidence of grade 3-4 febrile neutropenia with pixantrone vs. 3.0% in the comparator arm) or cardiotoxicity.

Grade 1-4 Adverse Events

The table below lists the grade 1-4 adverse events which occurred in at least 10% of patients on either arm. Again, most events were due to bone marrow suppression or cardiotoxicity.

Table 15: Grade 1-4 Adverse Events in ≥ 10% of Patients

Grade 1-4 Adverse Events	Pixantrone N = 68		Comparator N = 67	
	Gr 1-4	Gr 3-4	Gr 1-4	Gr 3-4
All	66 (97.1%)	52 (76.5%)	61 (91.0%)	35 (52.2%)
Neutropenia	38 (55.9%)	32 (47.1%)	17 (25.4%)	14 (20.9%)
Anemia	23 (33.8%)	7 (10.3%)	24 (35.8%)	10 (14.9%)
Leukopenia	18 (26.5%)	17 (25.0%)	7 (10.4%)	5 (7.5%)
Thrombocytopenia	18 (26.5%)	10 (14.7%)	15 (22.4%)	9 (13.4%)
Pyrexia	16 (23.5%)	3 (4.4%)	17 (25.4%)	6 (9.0%)
Asthenia	15 (22.1%)	3 (4.4%)	9 (13.4%)	3 (4.5%)
Cough	15 (22.1%)	0	3 (4.5%)	0
Ejection Fraction Decreased[1]	14 (20.6%)	1 (1.5%)	7 (10.4%)	0
Nausea	12 (17.6%)	0	10 (14.9%)	1 (1.5%)
Abdominal Pain	11 (16.2%)	5 (7.4%)	6 (9.0%)	3 (4.5%)
Peripheral Edema	10 (14.7%)	0	4 (6.0%)	0
Alopecia	9 (13.2%)	N/A	3 (4.5%)	N/A
Anorexia	9 (13.2%)	2 (2.9%)	5 (7.5%)	1 (1.5%)
Dyspnea	9 (13.2%)	4 (5.9%)	10 (14.9%)	3 (4.5%)
Fatigue	9 (13.2%)	2 (2.9%)	9 (13.4%)	0
Mucosal Inflammation	9 (13.2%)	0	3 (4.5%)	1 (1.5%)
Constipation	8 (11.8%)	0	3 (4.5%)	0
Skin Discoloration	7 (10.3%)	0	0	0
Vomiting	5 (7.4%)	0	10 (14.9%)	2 (3.0%)
Diarrhea	3 (4.4%)	0	12 (17.9%)	0

[1]Includes patient 118, coded as LV dysfunction but with decreased EF only.

Table 16 provides the grade 1-4 adverse events in ≥ 10% of patients in the entire pixantrone safety database and in the patients who received pixantrone at the proposed dose and schedule. Adverse events were not graded for patients who participated in some of the Phase 1 studies. Thus, only grade 1-4 adverse events are provided for the entire safety database (N = 348). Among the 111 patients who received pixantrone at the proposed dose and schedule, AEs were not graded in 10 patients. The safety analysis in this population was performed in 101 patients. Note that the adverse events in the safety database are similar to those in the randomized trial, but that some events such as, fatigue, nausea, and alopecia have an increased incidence in the safety database.

Table 16: Grade 1-4 Adverse Events in the Pixantrone Safety Database (≥10% Patients)			
Grade 1-4 Adverse Events	Any Pixantrone N = 348	Pixantrone 85 mg/M^2 d 1, 8, 15, q 28 d N = 101	
	Gr 1-4	Gr 1-4	Gr 3-4
All	342 (98.3%)	99 (98.0%)	82 (81.2%)
Neutropenia	218 (62.6%)	64 (63.4%)	51 (50.5%)
Leukopenia	191 (54.9%)	41 (40.6%)	33 (32.7%)
Lymphopenia	151 (43.4%)	28 (27.7%)	27 (26.7%)
Fatigue	150 (43.1%)	30 (29.7%)	13 (12.9%)
Nausea	136 (39.1%)	23 (22.8%)	0
Alopecia	120 (34.5%)	15 (14.9%)	N/A
Asthenia	93 (26.7%)	29 (28.7%)	5 (5.0%)
Thrombocytopenia	92 (26.4%)	26 (25.7%)	12 (11.9%)
Constipation	89 (25.6%)	15 (14.9%)	0
Chromaturia	87 (25.0%)	4 (4.0%)	0
Vomiting	85 (24.4%)	10 (9.9%)	0
Pyrexia	83 (23.9%)	22 (21.8%)	3 (3.0%)
Skin Discoloration	76 (21.8%)	10 (9.9%)	0
Diarrhea	72 (20.7%)	10 (9.9%)	0
Abdominal Pain	71 (20.4%)	17 (16.8%)	5 (5.0%)
Mucosal Inflammation	60 (17.2%)	13 (12.9%)	0
Ejection Fraction Decreased[1]	56 (16.1%)	19 (8.8%)	3 (3.0%)
Headache	55 (15.8%)	6 (5.9%)	0
Anorexia	54 (15.5%)	10 (9.9%)	2 (2.0%)
Cough	53 (15.2%)	19 (18.8%)	0
Dyspnea	53 (15.2%)	23 (22.8%)	7 (6.9%)
Weight Decreased	48 (13.8%)	8 (7.9%)	1 (1.0%)
Peripheral Edema	41 (11.8%)	13 (12.9%)	1 (1.0%)
Back Pain	37 (10.6%)	7 (6.9%)	0
Dizziness	37 (10.6%)	7 (6.9%)	0
Febrile Neutropenia	37 (10.6%)	7 (6.9%)	5 (5.0%)
Dyspepsia	35 (10.1%)	4 (4.0%)	0

[1]Includes cardiac function test abnormal, cardiac disorder (AZA II-01), and PIX301 patient 118, coded as LV dysfunction but with decreased EF only.

Laboratories

Grade 3-4 neutropenia occurred in 55.9% of patients on the pixantrone arm and 26.2% of patients on the comparator arm. Grade 3-4 thrombocytopenia was similar in both arms. The increase in grade 3-4 neutropenia, dose delays or reductions, use of G-CSF, and, more importantly, the percentage of patients with febrile neutropenia suggests that the proposed dose of pixantrone may not be optimal.

Cardiotoxicity

Given the increase in cardiac events as well as the drug class, the cardiotoxicity of pixantrone was examined further. The table below provides information on cardiotoxicity in the Phase 3 trial while Table 18 provides information on cardiotoxicity in the safety database. Patients entering the Phase 3 study had received prior anthracyclines/anthracenediones. Most patients

had baseline EF ≥ 50% by MUGA. However, 2 patients on the pixantrone arm and 3 on the comparator arm had baseline EF < 50%. Neither of the pixantrone-treated patients with baseline EF < 50% had an on-therapy MUGA and both died of PD.

Table 17: Cardiotoxicity in the Phase 3 Trial

	Pixantrone N = 68		Comparator N = 67	
Cardiotoxicity	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
All	22 (32.4%)	2 (2.9%)	16 (23.9%)	0
Arrhythmias	6 (8.8%)	0	8 (11.9%)	0
Cardiac Dysfunction	17 (25.0%)	2 (2.9%)	8 (11.9%)	0
Heart Failure[1]	4 (5.9%)	1 (1.5%)	1 (1.5%)	0
EF Decreased[2]	14 (20.6%)	1 (1.5%)	7 (10.4%)	0
Ischemia	1 (1.5%)	1 (1.5%)	1 (1.5%)	0

[1]Includes cardiac failure, congestive cardiac failure, and congestive cardiomyopathy.
[2]Includes patient 118, coded as LV dysfunction but with decreased EF only.

Two patients on the Phase 3 trial had heart failure events during the follow-up period that were not included in the updated AE dataset, but have been added to the table. Patient 87 on the pixantrone arm had an SAE of heart failure at 12 months follow-up after subsequent therapy. Patient 110 on the comparator arm had heart failure at 6 months follow-up after developing infectious myocarditis followed by cardiac fibrosis. Neither of these cardiac failure events was assigned a toxicity grade.

Although no patients on the comparator arm experienced grade 3-4 cardiotoxicity, grade 5 cardiac failure was reported for 1 patient.

Table 18: Cardiotoxicity in the Safety Database

Cardiotoxicity	Any Pixantrone N = 348	Pixantrone 85 mg/M^2 d 1, 8, 15, q 28 d N = 101	
	Gr 1-4	Gr 1-4	Gr 3-4
All	86 (24.7%)	28 (27.7%)	6 (5.9%)
Arrhythmias	27 (7.8%)	7 (6.9%)	0
Cardiac Dysfunction	67 (19.3%)	23 (22.8%)	5 (5.0%)
Heart Failure[1]	14 (4.0%)	6 (5.9%)	3 (3.0%)
EF Decreased[2]	56 (16.1%)	19 (18.8%)	3 (3.0%)
Ischemia	1 (<1%)	0	0
Troponin T Increased	3 (<1%)	0	0
Other[3]	2 (<1%)	1 (1.0%)	1 (1.0%)

[1]Includes cardiac failure, congestive cardiac failure, and congestive cardiomyopathy.
[2]Includes cardiac function test abnormal, cardiac disorder (AZA II-01), and PIX301 patient 118, coded as LV dysfunction but with decreased EF only.
[3]Includes pulmonary congestion, pulmonary edema

The table above provides information on cardiac events in the entire safety database (N = 348) and in patients who received the proposed dose and schedule (N = 101). Patients on the Phase 2 study are included in this latter group. Patients entering the Phase 2 study may have received prior anthracyclines or anthracenediones, but were required to have an EF ≥ 30%. Twenty-four patients had an EF ≥ 50% and 9 patients had an EF between 30 and 50%. Two patients with baseline EF between 30 and 50% experienced a ≥ 10% decline, one of whom also experienced grade 3 congestive heart failure and was withdrawn from study due to decreased EF. Given

the small number of patients on the Phase 2 study, the incidence of cardiac dysfunction is similar to that on the Phase 3 trial while the rate of cardiac dysfunction in the Phase 3 trial is higher than that of the safety database as a whole.

Table 19: Ejection Fraction and Troponin T in the Phase 3 Trial		
	Pixantrone	Comparator
Ejection Fraction	N = 64	N = 64
≥ 10% Decrease from Baseline	16	6
≥ 10% Decrease to < 50%	12	1
Troponin T	N = 50	N = 48
Grade 1-3	19 (38.0%)	6 (12.5%)
Grade 3	4 (8.0%)	2 (4.2%)

The above table provides additional information on decreases in ejection fraction in the Phase 3 trial. Ejection fractions, by MUGA, and troponins were assessed every 2 cycles. The above table includes Phase 3 patients with a baseline MUGA. If only patients with a follow-up MUGA (who can therefore be assessed for a decrease in EF from baseline) are considered, 16/41 (39%) on the pixantrone arm and 6/33 (18%) on the comparator arm had a ≥ 10% decrease in EF from baseline.

Troponin T may not indicate or may be a late indicator of cardiac damage and may reflect prior anthracycline/anthracenedione use (Expert Opin Metab Toxicol 2005 1:715). However, while the median prior exposure to anthracyclines/anthracenediones was higher in the comparator arm, a clear increase in troponin T levels can be seen in the pixantrone arm. Further, while grade 3 increases in troponin T are unusual in the literature, they occurred in both arms of this study. This may reflect the extensive prior anthracycline/anthracenedione exposure of these patients as well as ongoing exposure to pixantrone.

All of this suggests that pixantrone is indeed cardiotoxic, but no conclusions can be drawn concerning its toxicity relative to other anthracyclines/anthracenediones.

5. Issues for ODAC

- The randomized study was stopped at less than 50% of its planned accrual because of poor accrual. Do the efficacy data support accelerated approval of pixantrone for the proposed indication?

- Is the risk:benefit ratio favorable for the proposed indication?